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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,245	BURGIN ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 May 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/29/02, 11/18/02*, *10/21/02*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-9 are pending in the application.

[2] Applicants' amendment to the claims, filed July 29, 2004, is acknowledged.

Election/Restriction

[3] Applicants' election without traverse of Group III, claims 1-9, drawn to a crystal composition comprising a ternary complex and optionally wherein the crystal is Form 9, filed July 29, 2004, is acknowledged.

[4] Claim 9 is being examined only to the extent the claim reads on the elected subject matter.

Priority

[5] Applicant's claim for domestic priority under 35 USC § 119(e) to provisional application number 60/248,474, filed November 14, 2000 is acknowledged. Crystals having crystal structures of Forms 7-10 are disclosed in the provisional application (see particularly pp. 7-12 of application 60/248,474).

Information Disclosure Statement

[6] All references cited in the information disclosure statements (IDSs) filed 10/21/02, 11/18/02, and 11/29/02 have been considered by the examiner. A copy of each IDS is attached to the instant Office action.

Oath/Declaration

[7] The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration. See particularly the residence address for inventor Hidong Kim. It is noted that a similar correction should be made to the post office address for inventor Hidong Kim. See 37 CFR 1.52(c).

Sequence Compliance

[8] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment

directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly Figure 9.

Drawings

[9] The drawings are objected to as Figure 14 is not identified by a figure number.

Specification/Informalities

[10] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: --Crystallization of a Ternary Complex of Topoisomerase, Topoisomerase Inhibitor, and DNA--.

Claim Objections

[11] Applicant is advised that should claim 5 be found allowable, claim 6 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

[12] Claim 9 is objected to as reciting non-elected subject matter, *i.e.*, "Form 7," "Form 8," "Form 10," and "Form 11."

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[13] Claim(s) 1-6 and 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 1 (claim 2 dependent therefrom) is unclear in the recitation of "a ternary complex of a compound." In light of the specification, it would appear that the claim is intended to be drawn to a crystal composition of a ternary complex, wherein the ternary complex comprises a compound, a protein, and a poly-nucleic acid. The claim has been examined accordingly. It is suggested that applicants clarify the meaning of the claim.

[b] Claims 1 (claim 2 dependent therefrom) and 3 (claims 4-6 dependent therefrom) are unclear in the recitation of "poly-nucleic acid." It is suggested that applicants clarify the meaning of the term.

[c] Claims 2, 4-6, and 8-9 are indefinite in the recitation of "[a] crystal composition" (claims 2, 4-6, and 8) and "[t]he crystal composition" (claim 9). It is unclear as to why claims 2, 4-6, and 8 recite "[a] crystal composition" while claim 9 recites "[t]he crystal

composition." It is suggested that the indefinite term "[a] crystal composition" in claims 2, 4-6, and 8 be replaced with, for example, the definite term "[the] crystal composition."

[d] Claims 5-6 recite the limitation "the nucleic acid." There is insufficient antecedent basis for this limitation in the claim.

[e] Claim 9 is indefinite in the recitation of "Form 9" as it is unclear as to the crystal structures that are encompassed by this term. For example, does "Form 9" refer to space group symmetry, unit cell dimensions, both, or none of these ? It is acknowledged that non-limiting definitions of "Form 9-TTC" and "Form 9-AG260" are provided in the specification (p. 8), however, no definition of the term "Form 9" is disclosed. It is suggested that, for example, applicants clearly identify the crystal structure(s) that are encompassed by the term "Form 9" by identifying distinguishing characteristics of the crystal structure, *e.g.,* space group symmetry and unit cell dimensions.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[14] Claim(s) 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim(s) 1-9 are drawn

to a genus of crystal compositions comprising a compound, a protein, and a nucleic acid, optionally wherein the compound is a topoisomerase inhibitor, the protein is a eukaryotic topoisomerase or a human topoisomerase I, and the nucleic acid is duplex DNA, and optionally wherein the crystal structure is Form 9.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only five representative species of the recited genus of crystal compositions of a ternary complex of claims 1-8, *i.e.,* crystal compositions of ternary complexes of amino acids 175-765 of human topoisomerase allegedly disclosed in Stewart et al. (*J Biol Chem* 271:7593-7601; cited in the IDS filed November 18, 2002 as reference 26) complexed with oligos as set forth in Figure 9 and topoisomerase inhibitors topotecan, AG260, MJ-II-38, and Hoechst-33342 disclosed as Crystal Forms 7, 8, 9TTC, 9AG260, 10, and 11 (see pp.

14-15 and 17, Table I) and only two representative species of the recited genus of crystal compositions of a ternary complex of claim 9, *i.e.*, crystal compositions of ternary complexes of amino acids 175-765 of human topoisomerase allegedly disclosed in Stewart et al. (*J Biol Chem* 271:7593-7601; cited in the IDS filed November 18, 2002 as reference 26) complexed with oligos as set forth in Figure 9 and topoisomerase inhibitors topotecan and AG260 disclosed as Crystal Forms 9TTC and 9AG260 (see pp. 14-15 and 17, Table I). The specification fails to describe any additional representative species of the recited genus of crystal compositions as encompassed by the claims. In this case, the five representative species of the genus of claimed crystal compositions fail to describe the genus, which encompasses *widely* variant species with respect to protein, nucleic acid, and compound. That the genus encompasses widely variant species is evidenced by applicants' specification, which indicates that among the five ternary complex crystals, crystals having four different space group symmetries were identified. Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[15] Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a crystal of ternary complexes of amino acids 175-765 of human topoisomerase allegedly disclosed in Stewart et al. (*J Biol Chem* 271:7593-7601; cited in the IDS filed November 18, 2002 as reference 26) complexed with oligos as set forth in Figure 9 and the topoisomerase inhibitors topotecan and

AG260 having crystal structures as disclosed as Crystal Forms 9TTC and 9AG260 (see pp. 14-15 and 17, Table I), prepared according to the methods at pages 21-23 of the specification, does not reasonably provide enablement for any crystal composition as broadly encompassed by the claims prepared using any crystallization method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: Claim 1 is so broad as to encompass a crystal composition of any protein complexed with any compound and any nucleic acid, wherein the protein is covalently bound to a phosphorous of the nucleic acid. Claim 3 is so broad as to encompass a crystal composition of a complex of any compound and any topoisomerase covalently linked to any nucleic acid. Claim 7 is so broad as to

encompass a crystal composition of a complex of any compound and any human topoisomerase I covalently linked to any duplex DNA. It is acknowledged that claims 2, 4-6, and 8-9 further limit the protein, compound, nucleic acid, or the crystal structure of the crystal structure of the crystal. However, the specification fails to enable even the inventions of these claims. The protein, topoisomerase, or human topoisomerase I of the claims broadly encompasses not only wild-type proteins, but further encompasses mutants, variants, and fragments thereof. The compound or topoisomerase inhibitor encompasses compounds having any structure. The nucleic acid or duplex DNA can be of any composition and length. With the exception of claim 9, the crystals can have any crystal structure. Moreover, the crystals can be prepared by any method. The broad scope of claimed crystal compositions is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of crystals broadly encompassed by the claims. In this case the disclosure is limited to a crystal of ternary complexes of amino acids 175-765 of human topoisomerase allegedly disclosed in Stewart et al. (*J Biol Chem* 271:7593-7601; cited in the IDS filed November 18, 2002 as reference 26) complexed with oligos as set forth in Figure 9 and the topoisomerase inhibitors topotecan and AG260 having crystal structures as disclosed as Crystal Forms 9TTC and 9AG260 (see pp. 14-15 and 17, Table I), prepared according to the methods at pages 21-23 of the specification.

- The lack of guidance and working examples: The specification provides the working examples of a crystal of ternary complexes of amino acids 175-765 of human topoisomerase allegedly disclosed in Stewart et al. (*J Biol Chem* 271:7593-7601; cited

in the IDS filed November 18, 2002 as reference 26) complexed with oligos as set forth in Figure 9 and the topoisomerase inhibitors topotecan and AG260 having crystal structures as disclosed as Crystal Forms 9TTC and 9AG260 (see pp. 14-15 and 17, Table I), prepared according to the methods at pages 21-23 of the specification. These working examples fail to provide the necessary guidance for making the entire scope of crystal compositions broadly encompassed by the claims. For example, the specification fails to provide guidance regarding crystallization of other proteins complexed with other compounds using other methods of crystallization with an expectation of obtaining diffraction quality crystals.

- The high degree of unpredictability in the art is supported by the state of the art: Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that protein crystallization is usually quite difficult to achieve and the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Branden et al. teach that even small changes in the crystallization parameters, *e.g.,* pH, can cause the molecules to pack in different ways to produce different crystal forms (page 375, bottom). Thus, even minor modifications to a crystallization method may result in crystals that are distinct in structure having different space group symmetry and unit cell dimensions. At least in view of the teachings of Branden et al. a skilled artisan would recognize the high degree of unpredictability in generating the broad scope of claimed crystals.

- The amount of experimentation required is undue: While methods of protein crystallization are known, it is *not* routine in the art to make all crystals as broadly encompassed by the claims.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high degree of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use all crystal compositions as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[16] Claim(s) 1, 3-7, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Redinbo et al. (*Science* 279:1504-1513; cited as reference 7 in the IDS filed October 21, 2002). The claims are drawn to a crystal composition comprising a compound, a protein, and a poly-nucleic acid. Redinbo et al. teach a crystal of a fragment of human topoisomerase I covalently bound to a phosphorous of duplex DNA with water molecules associated with the crystallized topoisomerase. This anticipates claims 1, 3-7, and 9 as written.

It is noted that the term "compound" has not been defined in the specification. As such, in accordance with MPEP 2111, the examiner has provided the term "compound" with its broadest reasonable interpretation as encompassing a water molecule.

Conclusion

[17] Status of the claims:

- Claims 1-9 are pending.
- Claims 1-9 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 6:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 872-9306. Draft or

informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1652
09-01-04